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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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NIKAIDO MARMELSTEIN MURRAY & ORAM
METROPOLITAN SQUARE
SUITE 330 G STREET LOBBY
655 FIFTEENTH STREET NW
WASHINGTON DC 20005-5701

EXAMINER	
RICIGLIANO, J.	
ART UNIT	**PAPER NUMBER**
1615	15

DATE MAILED: 07/07/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/776,190	Josel et al.
Examiner	**Group Art Unit**
Joseph W. Ricigliano Ph. D.	1618

☒ Responsive to communication(s) filed on *Mar 29, 1999*.

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *39-62 and 64-71* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *39-62 and 64-71* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

KEITH D. MacMILLAN
PRIMARY EXAMINER

--- *SEE OFFICE ACTION ON THE FOLLOWING PAGES* ---

Amendments Entered

1. Applicants' amendment and response, paper number 14, filed 3/29/99 have been entered. Claims 1-38 have been canceled previously. Claim 63 has been canceled by the amendment of 8/19/98.

Claims 39-62, and 64-70 are pending in this application.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claim 39-62, and 64-70 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

4. Claims 39-62, and 64-70 and newly added claim 71 are rejected for reciting a peptide nucleic acid. The recitation is unclear because the specification at page 7 recites a peptide nucleic acid has a backbone made of the same or different monomeric units of a given formula and also that peptide nucleic acids have and their production are described in WO92/20703. The WO reference clearly embodies far more embodiments than the formula recited. Therefore, it is not possible to determine the metes and bounds of the invention as claimed.

Applicants argue that during the personal interview it was made clear that the specification clearly limits the PNA molecules to those having the recited formula.

In response to applicants' argument it is noted that although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The claim remains indefinite as it is unclear what the metes and bounds of the subject matter are which applicants are claiming.

Claim 56 is recites that a hapten can be selected from a group of molecules including metabolites and mediators. Metabolites and mediators are vague and indefinite because it is unclear what they metabolites are formed from and what limitations apply to "metabolites" or "mediators." Therefore, it is not possible to determine the metes and bounds of the invention as claimed.

Applicants' amendment which deleted the term mediator is noted. Applicants argue that a metabolite is "a substance reacted in biological metabolism" and that one of skill in the art would clearly understand this term. Applicants' argument has been considered but is not found persuasive because one of skill in the art would not be able to determine for any potential hapten if it was a "metabolite" of a known compound at least in part because it would require being able to predict the metabolic out come of presenting any or every living organism any compound (potential hapten). Moreover, as metabolic profiles change in response to environmental conditions it would require predicting the metabolic profile of any organism under every possible condition. Therefore, one of skill in the art would not be able to determine the metes and bounds of the claim or know if they were infringing on the claimed subject matter.

5. Claims 60-62 and 64-65 recite one of the following steps (a) and (b) are conducted. This is vague and indefinite because it is unclear what steps are to be conducted. Therefore, it is not possible to determine the metes and bounds of the invention as claimed.

Applicants argue that during the personal interview it was made clear that either or both of the steps could be performed and that the scope of the invention is not indefinite, it merely suggests alternative ways in which the invention could be accomplished. This argument has been considered but is not found persuasive because the language of the claims has not been amended to reflect the use of steps a or b or both, which simply requires amending the language of the claim to recite "wherein at least one of steps(a) or (b) is conducted ..."

Prior Art Rejections Withdrawn

6. The rejection of claims 60 and 62 as being anticipated by Smith et al under 35 U.S.C. 102(b) and the rejection of claim 61 rejected under 35 U.S.C. 103(a) as being unpatentable over Smith *et al* in view of Buchardt have been withdrawn in view of applicants amendment which sets forth that the hapten molecules, marker groups solid phase binding groups are different from each other.

Claim Rejections - 35 USC § 103

7. Claims 39, 41-51, 55-62, 64-70 and newly submitted claim 71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Buchardt *et al* WO 92/20703 in view of Bredehorst *et al* (Analytical Biochemistry 193:272-279).

Buchardt *et al* teach the synthesis and use of peptide nucleic acids or PNA (which reads on nucleotide analogs) wherein the PNA is at made of at least 2 monomers (page 5 line 2), and in

a preferred embodiment the length is from 2-61 (page 7 line 10). Buchardt *et al* teach that PNA molecules may be conjugated to reporter ligands including: alkylators, fluorescent compounds, spin labels or protein recognition ligands such as biotin or haptens, which read on marker groups, haptens or solid phase binding groups coupled to reactive side chains (page 20 starting at line 26). Moreover, Buchardt *et al* teach that the L groups (see figure III page 3 for example), which read on groups coupled to reactive side chains, can be a fluorophore, radio or spin label or protein-recognizing ligand such as biotin or a hapten (page 19 lines 5-8). In that each L group is specifically located on the molecule in a location which is determined by the synthetic process under the control of the researcher these groups must be at predetermined positions.

With respect to the dependent claims Buchardt *et al* teach that the oligomers of their invention can be from 2-61 monomers (see page 7, structure III and line 10) which reads on the limitations of claims 41 and 42. In that L groups are explicitly recited as being haptens or fluorophores and as many as 61 L groups are present in a recited preferred embodiment, Buchardt *et al* meet the limitations of claims 43- 44. Buchardt *et al* (which applicants recite as teaching PNA molecules at page 7 of their specification) specifically recite that the molecules of their invention are nucleic acid analogs (see page 1, first line of the specification), therefore, Buchardt *et al* read on the nucleotide analogs of claim 45, 46. Buchardt *et al* teach that the molecule of their invention may be used in a method of capturing a nucleic in a hybridization assay (page 9 line 14 to page 10 line 36), thus the conjugate must be present as a double strand reads on claims 47-48.

Buchardt teaches that the L groups are attached to "A" groups which read on the reactive side groups of the instant claims (see structures III-VI). "A" groups are defined on page 5 lines 11-36 as having amino and alkylthio substitutents and therefore read on the limitations of claims 49. In that L is specifically recited as being a fluorophore or biotin Buchardt *et al* read on claims 50 and 51. In that the L groups, which may be haptens as discussed above, are selected from groups including aromatic moieties, which includes simple molecules such as catechol, Buchardt *et al* renders obvious the inventions of claims 55 and 56 since catechol has a MW of 110 and is both a pharmacologically active compound and a neurotransmitter. Buchardt *et al* teach that the molecules of their invention can be conjugated to a peptide, protein or oligonucleotide which reads on the inventions of claim 57-59

Buchardt teaches the synthesis of PNAs (page 23 line 8 through page 27). Buchardt *et al* teach that the oligomers may be conjugated to, or that the L groups may be: markers, solid phase binding group or haptens (e.g. as discussed above, fluorophores, spin labels, radioactive labels, protein recognition ligands, biotin or haptens; page 20 lines 26-30). Buchardt teaches in reference to the incorporation of a detectable label "all those methods for labeling peptides, DNA and/or RNA which are presently known may in general terms be applied to PNA's" (page 14 lines 7-9) and the use of protecting groups in PNA synthesis (page 23 line 8 through page 27) and the use of protecting groups specifically associated with the L group (page 19 lines 9-14). Buchardt *et al* specifically teach modification of the terminal groups, one of which must be an amine, (page 20 lines 17-25). Therefore Buchardt *et al* reads on the inventions of claims 60-62 and 64-65.

Buchardt *et al* teach the formation of PNA DNA hybrids and PNA hybridization which reads on the immuno assays of claims 66-68 (page 13 -14). Buchardt teaches the ability to immobilize a PNA and to displace a strand of the complex and the incorporation of antigen labels which reads on a competitive immunoassay which read on claims 69 and 70.

Buchardt *et al* do not specifically teach that the peptide nucleic acids are helical as required by claim 54. However, in that the conjugates are drawn to the nucleic acid analogs known as peptides nucleic acids disclosed by Buchardt *et al* and that PNA molecules can hybridize to form double stranded molecules with other nucleic acids. Thus, since nucleic acids are known to hybridize into helical structures, it appears that PNA molecules must be inherently capable of forming this structure. Therefore, the burden is upon applicants to show an unobvious difference as required in MPEP 2112.

Buchardt *et al*, while teaching that multiple groups may be incorporated into or conjugated to a PNA molecule, does not explicitly recite incorporating both marker groups and haptens or solid phase binding groups into a single polymeric conjugate molecule.

However, Bredehorst *et al* teach the formation of carrier molecules (conjugates) formed from amino acids with both hapten and multiple marker molecules placed at specific positions see figure 1. In addition to the previously recited teaching it is noted the Bredehorst also teaches the use of the conjugates in immuno assays.

It would have been *prima facia* obvious to one of ordinary skill in the art at the time the invention was made to incorporate both hapten and marker molecules as taught by Bredehorst *et al* in a PNA which is nucleic acid analog as taught by Buchardt *et al* because Buchardt *et al* teach

the incorporation of haptens and markers into PNA molecules at selected sites and Bredehorst *et al* teach that is it known in the art to incorporate both a hapten and a marker into the same conjugate. One of ordinary skill in the art would have been motivated to do so in order to provide for a sensitive immuno assay of haptens which can quench the fluorophore markers without loss of sensitivity as taught by Bredehorst *et al*. One of ordinary skill in the art would have reasonably expected to be successful because the successful synthesis of PNA molecules incorporating multiple functionalities at specific positions and the incorporation haptens or markers had previously been taught by Buchardt *et al* and the required placement of a hapten at position distant enough to prevent quenching of the marker fluorophore would be readily achieved with a PNA molecule.

8. *Applicants argue that Bredehorst uses a naturally occurring peptide which contains specific reactive groups in a set stoichiometry, hence other advantageous stoichiometries cannot be obtained. Applicants also argue that the distance between the fluorescent marker groups is arbitrary. Applicants also assert that in Bredehorst there is no hint of how larger amounts of marker groups could be introduced and that it is disadvantageous that the marker groups can only be introduced afterwards.*

Applicants assert that Buchardt does not teach the incorporation of different haptens or marker groups or what measurements should be taken. Applicants assert the advantages of their invention by reference to example 4 which has two hapten molecules and two marker groups which they assert has considerably improved test performance with advantages that can be found when more than one hapten and more than one marker or solid phase binding group can be

found and have amended their claim language to recite the range of 2-10 haptens and 2-10 marker groups or solid phase binding groups.

Applicants *further assert that "only the instant procedure allows the concerted attachment of haptens and markers which is neither disclosed in the prior art and which applicants assert is not rendered obvious by the prior art. Applicants assert that by conventional labeling methods mixtures are obtained where as the instant method produces "uniform" conjugates. Applicants assert that until now the art has depended on statistical attachment to allow control of both the position and stoichiometry of haptens and markers and have provided a drawing with associated legends. In the legend the inventors state " Only the invention can lead to a predetermined and defined end product (conjugate), when two or more identical monomeric units are to be used," and go on to assert that the state of the art methods will only yield statistical mixtures.*

9. *Applicants' arguments have been considered but are not found persuasive as discussed below:*

Applicants' assertion that Bredehorst uses a naturally occurring peptide which having reactive groups in a set stoichiometry, hence other advantageous stoichiometries cannot be obtained is not found persuasive because haptens, marker group, and solid phase binding group limitations meet the limitations of the instant product claims. In addition the Buchardt reference teaches how to incorporate multiple independently selected L groups which as indicated in the discussion above can be haptens or marker groups. Moreover, the claim as amended requires

the introduction of 2-10 haptens and 2-10 marker groups or alternatively solid phase binding groups.

Applicants' further assertion that the distance between the fluorescent marker groups is arbitrary is not persuasive because the markers are set at specific positions on the insulin peptide and have specific distances between them. In addition the distance between any groups introduced in the synthesis of a PNA by the method of Buchardt would result in a defined distance as they would be synthesized by adding the groups during specific cycles at specified monomer position. Applicants' assertion that there is no hint of how larger amounts of groups and that it is disadvantageous that the marker groups can only be introduced afterwards are not found persuasive. First, with respect to the product claims arguing the method of making is moot as the products meet the limitations of the product claims. Second, with respect to the method of synthesis claims (60-62 and 64-65) it is noted that Bredehorst was not cited for teaching the method of synthesis, Buchardt was cited for this teaching. In addition the PNA synthesis method of Buchardt sets forth the ability to introduce up to 61 independently selected L groups. Hence, there is clear teaching on how to incorporate more groups in the references as combined. Moreover, it is noted that the independent claim drawn to the method of synthesis (claim 60) includes the introducing groups "after the synthesizing step" which applicants are now arguing is disadvantageous, hence applicants' arguments appear to be in conflict with their claims.

Applicants' assertion that Buchardt does not teach the incorporation of different haptens or marker groups or what measurements should be taken has been considered but is not found

persuasive because Buchardt teaches the L groups can be independently selected. Furthermore, Bredehorst et al was cited for the teaching that different groups should be incorporated in a conjugate. Applicants' assertion that Buchardt does not teach "what measurements should be made" it is noted that the claims do not recite specific measurements only competitive or non-competitive immuno (binding) assays and Bredehorst teaches the use of conjugates in immuno assays (e.g., figure 5).

With respect to the method of use claims 66-70 applicants assert advantages of their invention by reference to example 4 which has two hapten molecules and two marker groups which they assert has considerably improved test performance with advantages that can be found when more than one hapten and more than one marker or solid phase binding groups are attached. It is noted that Bredehorst et al teaches that increased sensitivity is found when using the conjugate recited therein (See column 1 page 277, "However, the sensitivity of the assay is significantly higher when DNP-Ins-Fl is used as labeled hapten.")

Applicants have also noted that they have amended their claims to recite the range of 2-10 haptens and 2-10 marker groups or solid phase binding groups, however, claim 71 which is newly submitted does not include such limitations.

Applicants' further assertion that "only the instant procedure allows the concerted attachment of haptens and markers which is neither disclosed in the prior art and which applicants assert is not rendered obvious by the prior art and that by conventional labeling methods mixtures are obtained where as the instant method produces "uniform" conjugate have also been considered and not found persuasive. The argument is not found persuasive because

the examiner did not set forth a rejection based upon the "conventional techniques" but based upon the synthesis of PNA molecules by Buchardt. The method described by Buchardt would yield uniform molecules with predetermined positions modified and not mixtures resulting from stochastic addition to multiple site.

With respect to the figure prepared by applicants and its attached legend in which applicants' specifically state " Only the invention can lead to a predetermined and defined end product (conjugate), when two or more identical monomeric units are to be used." and go on to assert that the "state-of-the-art" methods will only yield statistical mixtures. It is noted that the instant invention is not limited to the use of two or more identical monomers. Moreover, applicants have failed to address why the introduction of haptens, markers and solid phase binding groups by the method of Buchardt et al, which was cited for the teaching of PNA synthesis, which is a "state-of-the-art-procedure," would not result in the instant claimed invention and would result in a mixture.

10. Claims 40, 50 and 52-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Buchardt et al in view of Bredehorst and further in view of Bard et al.[US 5,310,687, filed 11/4/98].

See the teaching of Buchardt et al as applied to claims 39, 41-52, 54-62, and 64-70 under 35 U.S.C. 103(a) as being unpatentable over Buchardt et al in view of Bredehorst et al supra.

In addition to the teachings above Bredehorst et al specifically recite the incorporation of negatively charge groups (i.e., SO3-, see figure 1) and the use of amino acid based conjugates

and Buchardt et al teach the attachment of positive charged (polylysine) and negative charged (carboxyl or sulfo groups) to the carrier molecule; page 20 lines 17-25.

Buchardt et al in view of Bredehorst et al do not teach the use of luminescent metal chelates as required in an alternative embodiment in claim 50 or as a specific limitation of claims 40 and 52-54.

However, Bard et al teach the use of luminescent metal chelates as a marker with superior properties for use in assays (See the summary of the invention starting in column 5).

It would have been prima facia obvious to one of ordinary skill in the art at the time the invention was made use the luminescent metal chelates of Bard et al et al in the conjugates as taught by Buchardt et al in view of Bredehorst et al because Buchardt et al in view of Bredehorst et al teach the incorporation of marker groups into conjugates for immuno assays and Bard et al teach the incorporation of luminescent metal chelates into molecules for detecting analyte in immuno assays formats. One of ordinary skill in the art would have been motivated to incorporate the luminescent metal chelates of Bard et al in conjugates as taught by Buchardt et al in view of Bredehorst et al in order to take advantage of the rapid efficient and sensitive detection permitted by the chemiluminescent markers taught by Bard et al (see abstract). One of ordinary skill in the art would reasonably have expected to be successful because Bard et al had previously incorporated and applied the chemiluminescence metal chelates to a variety of assays including immunoassay.

11. Therefore, claims 39-62, and 64-70 remain rejected for the reasons above and for the reasons of record in paper number 11.

New *Grounds of Rejection*

Claim Objections

12. Claim 71 is objected to because of the following informalities: Claim 71 recites that "the monomeric units are at least one member selected from..." instead of "the monomeric units have at least one member selected form." Appropriate correction is required.

13. Claim 68 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicants are required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 68 recites that more than one hapten is present and used as poly hapten. As applicants have amended the independent claim from which it depends (39) to recite 2-10 haptens are present this claim fails to further limit the invention.

Claim Rejections - 35 USC § 112

14. Claims 40, 52, 60-62 and 64-65 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 40 and 52 recite that the solid phase binding groups are luminescent metal binding chelates, which does not appear to be supported by the disclosure as originally filed. Applicants can overcome this rejection by indicating where support can be found in the disclosure as originally filed.

Claims 60-62 and 64-65 have been amended to recite that the method may be accomplished without cleavage of protecting groups (see page 14 of the 3/29/99 response). Applicants have stated that support can be found in the specification as filed but have not indicated where support is to be found. Applicants can overcome this rejection by indicating by line and page number where support can be found in the disclosure as ordinally filed.

Claim Rejections - 35 USC § 102

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

16. Claims 39, 41-44, 49 and 71 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Bredehorst [Anal. Biochem. 193:272-279 (1991)].

It is noted by the examiner that this rejection is being specifically made in response to applicants amendment to include amino acids as monomers. It is further noted that the former rejection over Bredehorst was withdrawn over applicants' arguments presented in the response of August, 1998 (paper number 10, pages 2-3) that the Bredehorst rejection should be withdrawn

since the reference did not include the monomers recited in the claim (i.e., Bredehorst used amino acid monomers).

Bredehorst et al in figure 1 teach a polymeric carrier (insulin) having 21 amino acids coupled to three fluorescein molecules which are haptens, and three solid phase binding groups SO_3. (Which can interact with anion exchange resins for example) and a DNP molecule which is also a solid phase binding group based upon the fact that it can be used to immobilize the molecule with anti-DNP antibodies (see figure 4). As the hapten molecules and solid phase binding molecules are different and are introduced at specific positions, they are in predetermined locations, hence Bredehorst anticipates claims 39 and 71. [It is noted that DNP and fluorescein can fill the role of solid phase binding groups, markers or haptens. As both the DNP and fluorescein molecules can be markers because of their spectral properties, solid phase binding groups when the solid phase is modified to contain antibodies against them and are known haptens (See attached Sigma catalog which evidences that DNP and fluorescein are haptens with known antibodies.)]

In addition, as Bredehorst discloses a peptide with three SO3 and three fluorescein groups, Bredehorst discloses a polymeric carrier having solid phase binding groups.

With respect to the dependent claims:

As insulin has 21 amino acids Bredehorst et al anticipate the limitations of claims 41 and 42. As the conjugate incorporates three hapten molecules it anticipates the invention of claims 43, 44. As the SO_3- groups are attached to Cys residues which have a thiol side group Buchardt et al anticipate claims 49.

Conclusion

17. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph W. Ricigliano Ph. D. whose telephone number is (703) 308-9346. The examiner can be reached on Monday through Thursday from 7:00 A.M. to 5:30 P.M.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the group receptionist whose telephone number is (703) 308-0196.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Donald E. Adams Ph. D., can be reached at (703) 308-0570.

KEITH D. MacMILLAN
PRIMARY EXAMINER

Joseph W. Ricigliano Ph. D.